PATENT COOPERATION TREATY

REC'D 14 JUL 2004
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4 -32584A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/08179	International filing date *(day/month/year)* 24.07.2003	Priority date *(day/month/year)* 25.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/22		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.01.2004	13.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hedegaard, A Telephone No. +49 89 2399-8644

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/08179

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-35 as originally filed

Claims, Numbers

1-16 received on 14.06.2004 with letter of 10.06.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 15

   because:

   ☒ the said international application, or the said claims Nos. 15 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-14, 16
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Section III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claim 15 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability, novelty and inventive step of the subject-matter of said claim (Article 34(4)(a)(i) PCT).

Re Section V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: WO-A-9815264
   D2: EP-A-0465096

   If not indicated otherwise, the relevant passages are those mentioned in the International Search Report.

   D1 discloses compositions for sustained release comprising fluvastatin sodium and a matrix based on hydrophilic and/or hydrophobic matrix forming excipients. Example 5.4 of D1 discloses a process for making fluvastatin tablets in which a dry mix (inner phase) of fluvastatin, HPMC, sodium aluminium silicate and carboxypolymethylene is granulated with ethyl cellulose (outer phase) in ethanol. The granulate is dried and compressed to tablets.

   D2 discloses sustained release tablets comprising lovastatin or simvastatin and HPMC. Examples 12-14 show tablets comprising simvastatin, HPC and HPMC (Methocel E4MCR and Methocel K15MCR) as an inner phase and being coated with a mixture comprising HPMC 6 cps and HPC LF-NF (outer phase).

2. The subject-matter of independent claims 1, 17 and 18 is novel (Art. 33(2) PCT) since compositions for sustained release comprising pitavastatin and an inner and an outer phase has not been disclosed in the available prior art documents.

3. D1 and D2 disclose compositions for sustained release comprising HMG-CoA reductase inhibitors, an inner phase and an outer phase comprising at least one matrix former. The subject-matter of present claim 1 differs therefrom only in specifying that the HMG-CoA reductase inhibitor is pitavastatin. However, this modification does not appear be accompanied by any non-obvious effects and can be carried out by the person skilled in the art without having to resort to inventive skill. Therefore, the subject-matter of claim 1 is not considered to involve an inventive step (Art. 33(3) PCT).

4. The same applies mutatis mutandis to independent claims 15 and 16.

5. Having regard to the disclosures of D1 and D2, dependent claims 2-14 do not appear to contain inventive features and are only allowable when related to an independent claim which fulfils the requirements of the PCT.

6. For the assessment of the present claim 15 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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   because:

   ☒ the said international application, or the said claims Nos. 15 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-14, 16
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Section III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claim 15 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability, novelty and inventive step of the subject-matter of said claim (Article 34(4)(a)(i) PCT).

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What is claimed is

1. A pharmaceutical composition for sustained release comprising as active ingredient pitavastatin or a pharmaceutically acceptable salt thereof, said composition comprising an inner phase (internal) and an outer phase (external), wherein at least the outer phase comprises at least one matrix former.

2. A composition according to claim 1 wherein the amount of HMG-CoA reductase inhibitor or pharmaceutically acceptable salt thereof is about 5-50 weight % of the composition.

3. A composition according to anyone of claims 1 to 2 wherein the amount of HMG-CoA reductase inhibitor or pharmaceutically acceptable salt thereof is about 1-32mg.

4. A composition according to anyone of claims 1 to 3, wherein the inner phase comprises a matrix former .

5. A composition according to claim 4, wherein the matrix former of the inner phase comprises one or more types of matrix former component having different viscosities.

6. A composition according to claim 5, wherein the matrix former of the inner phase has a viscosity of about 1 to about 500 cps.

7. A composition according to any one of claims 1 to 6, wherein the matrix former of the external phase comprises one or more type of matrix former component having different viscosities.

8. A composition according to claim 7 , wherein the matrix former of the external phase has a viscosity of about 100 to about 100000cps.

9. A composition according any one of claims 1 to 8, wherein the matrix former is selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydrophilic polymers such as hydroxypropylcellulose, hydroxymethylcellulose, and hydroxypropylmethylcellulose or the like.

10. A composition according to claim 9, wherein the matrix former is hydroxypropylmethylcellulose (HPMC).

11. A composition according to claim 10 wherein the amount of HPMC as a matrix former is about 1-60 weight % of the composition.

12. A composition according to anyone of claims 1 to 11, wherein said composition comprises a stabilizer .

13. A composition according to claim 12, wherein the stabilizer is magnesium aluminium metasilicate (neusilin).

14. A composition according to claim12 or 13, wherein the amount of the stabilizer is about 1-15 weight % of the composition.

15. A method of treatment of hyperlipidemia, hypercholesterolemia and atherosclerosis, as well as other diseases or conditions in which HMG-CoA reductase is implicated comprising administering to a patient in need thereof a therapeutically effective amount of a composition according to any one of claims 1 to 14.

16. Use of the composition according to any one of claims 1 to 14 in the manufacture of a medicament for use in the treatment or prevention of a cardiovascular disease, e.g., hypercholesterolemia, hyperproteinemia and /or atherosclerosis.